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REVIEW ARTICLE

Pharmacotherapy in Interstitial Cystitis / Painful Bladder Syndrome

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SUMMARY

Interstitial cystitis / Painful bladder syndrome is a chronic disease characterized by suprapubic pain associated with bladder filling, accompanied by an overactive detrusor and inflammation of the bladder. Although the etiology and pathophysiology of this disease are not unlightened yet, some pathophysiological theories such as the glycosaminoglycan theory, altered permeability, neural regulation, mast cell, and neuroendocrine theories have been suggested. Different treatment methods have been developed based on these theories. The developed pharmacotherapies can be classified as conservative treatment, oral treatment, intravesical treatment, and current treatment methods. Agents used in oral treatment include pentosan polysulfate sodium, tricyclic antidepressants, histamine receptor antagonists, immunosuppressants, and AQX-1125 (Rosiptor). Agents also used in intravesical therapy include dimethyl sulfoxide, lidocaine, heparin, pentosan polysulfate sodium, chondroitin sulfate, hyaluronic acid, and Bacillus Calmette-Guerin. The use of botulinum toxin A (BTX-A) has also been approved. Finally, current treatment methods include phosphodiesterase-5 inhibitors, monoclonal antibodies, cannabinoids, and liposomes use. The goal of most treatments is to control symptoms.

Keywords: *Interstitial cystitis / Painful bladder syndrome, inflammation, conservative treatment, oral treatment, intravesical treatment*

İnterstisyel Sistit / Ağrılı Mesane Sendromunda Farmakoterapi

ÖZ

İnterstisyel sistit/Ağrılı mesane sendromu, mesanenin dolu olmasına bağlı olarak suprapubik ağrı, aşırı aktif detrusor ve mesanenin inflamasyonu ile karakterize kronik bir hastalıktır. Bu hastalığın etiyolojisi ve patofizyolojisi kesin olarak bilinmemekle birlikte glikozaminoglikan teorisi, değişen geçirgenlik, nöronal düzenleme, mast hücresi ve nöroendokrin teorisi gibi gibi birçok patofizyolojik teori ileri sürülmüştür. Bu teoriler dikkate alınarak farklı tedavi yöntemleri geliştirilmiştir. Geliştirilen farmakoterapiler konservatif tedavi, oral tedavi, intravezikal tedavi ve yeni nesil tedavi yöntemleri olarak sınıflandırılabilir. Oral tedavide kullanılan ajanlar pentosan polisülfat sodyum, trisiklik antidepresanlar, histamin reseptör antagonistleri, immünosupresanlar ve AQX-1125 (Rosiptor); intravezikal tedavide kullanılan ajanlar ise dimetil sülfoksit, lidokain, heparin ve pentosan polisülfat sodyum, kondroitin sülfat ve hyaluronik asit, Bacillus Calmette-Guerindir. Botulinum toksin A (BTX-A) kullanımını da onay almıştır. Son olarak yeni nesil tedavi yöntemleri fosfodiesteraz-5 inhibitörleri, monoklonal antikorlar, kanabinoidler ve lipozom kullanımı gibi yöntemleri içermektedir. Tedavilerin birçoğunun hedefi semptomların kontrolünü sağlamaktır.

Anahtar Kelimeler: *İnterstisyel sistit / Ağrılı mesane sendromu, inflamasyon, konservatif tedavi, oral tedavi, intravezikal tedavi.*

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INTRODUCTION

INTERSTITIAL CYSTITIS / PAINFUL BLADDER SYNDROME (IC/PBS) PATHOPHYSIOLOGY

Interstitial cystitis / Painful bladder syndrome (IC/PBS) is a chronic inflammatory bladder syndrome characterized by a sudden urge to urinate together with painful micturition, increased urinary frequency, and bladder overreactivity. These symptoms of urinary urgency, urinary bladder pain, and irritative symptoms last more than 6 months (Zhao et al., 2016). Chronic inflammation observed in the bladder may directly affect its function.

Although the pathophysiological mechanisms underlying IC/PBS are not fully understood, several hypotheses have been proposed, including glycosaminoglycan (GAG) layer deficiency with increased epithelial permeability, microbial infection theory, mast cell activation, neurogenic or neuro-urothelial interactions, and autoimmune mechanisms (Patnaik et al., 2017). Among these, the most widely accepted hypothesis proposes that an initial defect or injury of the bladder mucosal barrier subsequently induces chronic inflammation. The urothelium exhibits a unique structural organization characterized by polysaccharides such as chondroitin sulfate, hyaluronic acid, and glycoproteins (Lewis, 2000). This configuration establishes a non-adhesive, highly impermeable barrier that protects the urothelium against bacterial adherence as well as urinary irritants. Structural disruption or biochemical deficiency within this barrier impairs its integrity, allowing urinary solutes to penetrate the suburothelial space of the bladder wall. The suburothelial compartments and the bladder wall (Parsons, 2011). Histopathological analyses of bladder biopsies from patients with IC/PBS have demonstrated aberrant expression of uroplakins, chondroitin sulfate, and tight junction proteins (Slobodov et al., 2004). Consequently, urinary constituents such as potassium ions may traverse the defective urothelium, inducing depolarization of muscle and neuronal cells, activating inflammatory signaling cascades, and provoking mast cell degranulation, thereby contributing to the pathogenesis of IC/PBS-associated lower urinary tract symptoms

Chronic inflammation has a role in the pathogenesis of IC/PBS. Biopsies from IC/PBS patients have demonstrated mast cell infiltration, leukocyte accumulation of inflammatory cells within the suburothelial layers and bladder wall, accompanied by increased vascularity and bladder wall thickening. The mechanisms underlying infection-induced pain are not fully understood, experimental studies have shown that stimulation with defective mutants of *E. coli* lacking in O-antigen biosynthesis may induce allodynia that persists long after the infection has been treated (Rudick et al., 2012). Therefore, IC/PBS may represent a sterile/chronic inflammatory condition triggered by a prior episode of microbial cystitis. The exact cause of IC/PBS remains unclear; however, it is widely accepted that multiple factors contribute to its pathophysiology.

As of yet, there are no other ways to study the effects of cystitis on the bladder comprehensively, including the changes in bladder structure and function, but to use animal models. Because the exact cause of IC/PBS in patients remains elusive, it is not possible to precisely reproduce the condition under experimental conditions. However, animal models have proven useful in investigating the underlying mechanisms of bladder inflammation and for evaluating potential therapeutic strategies to alleviate clinical symptoms. Rodents are the most widely used species used to study IC/PBS, and many models for inducing cystitis in rodents have been developed over the years, such as neurogenic cystitis caused by heat, cold, bacterial and viral infection, and antigen exposure. Intravesical instillation of irritants such as lipopolysaccharide (LPS), acids (hydrochloric acid and acetic acid), turpentine, mustard oil, croton oil, and acrolein is commonly used to induce experimental cystitis in rodents (Birder & Andersson, 2018). Cyclo-

phosphamide-induced IC/PBS is a well-established model in rodents that mimics some of the symptoms of this condition observed in humans, such as pain, inflammation, and increased urinary frequency and urgency. In experimental IC/PBS models induced by cyclophosphamide, contractile responses of detrusor smooth muscle to different agonists such as carbachol, trypsin, or sphingosine-1-phosphate are altered. Moreover, aging has been reported to change the detrusor function in these models (Anjum et al., 2017; Denizalti et al., 2018; Denizalti et al., 2022; Denizalti et al., 2023; Durlu-Kandilci et al., 2015; Masago et al., 2009). However, the exact cause of IC/PBS and how to treat bladder dysfunction in patients has not yet been identified.

PHARMACOLOGICAL TREATMENT APPROACHES

According to the American Urological Association's updated 2022 guideline, treatments for IC/PBS are categorized into four main groups: behavioral and non-pharmacological interventions, oral pharmacotherapy, intravesical therapies, and major surgical procedures. When necessary, concurrent and multimodal therapeutic approaches are recommended. The multimodal treatment strategy for IC/PBS should be based on the potential pathophysiological mechanisms of the disease. Given the multifactorial etiology of IC/PBS, achieving a satisfactory clinical response may require combining multiple therapeutic modalities targeting the underlying pathological processes. Multimodal treatment strategies grounded in the underlying pathophysiological mechanisms and clinical characteristics of IC/PBS may lead to more successful therapeutic outcomes. Therefore, it is emphasized that clinical management of IC/PBS should be individualized according to each patient's unique clinical profile (Clemens et al., 2022; Jhang et al., 2025).

Pharmacotherapy in IC/PBS is diverse, reflecting the multiple pathophysiological mechanisms underlying the disease. Mechanisms of bladder dysfunction include chronic bacterial infection, disruption of the glycosaminoglycan (GAG) layer, activation of mast cells, autoimmune-mediated mechanisms, and autonomic nervous system dysfunction. Research exists on treatment options targeting each of these mechanisms, but there is still no a definitive cure (Chen & Kuo, 2020). First-line treatment includes conservative, non-pharmacological approaches such as behavioral modifications, pelvic floor exercises, controlled fluid intake, and bladder training. Second-line treatment includes oral medication such as pentosan polysulfate, tricyclic antidepressants, histamine, and leukotriene receptor inhibitors, immunosuppressants, and AQX-1125 (Rosiptor), whereas third-line therapy involves intravesical administration (Garzon et al., 2020).

Conservative treatment (non-pharmacological management)

First-line treatment includes conservative management such as behavioral and dietary modifications, heat or cold therapy, pelvic floor exercises, and psychological stress reduction. Dietary restrictions, such as limiting the intake of coffee, tea, alcohol, chocolate, and spicy foods, have been shown to alleviate IC/PBS symptoms. In addition, proper regulation of diet and fluid intake helps reduce constipation and normalizes urinary frequency (Bosch & Bosch, 2014; Friedlander et al., 2012). Pelvic floor exercises (such as knee-chest position, legs-spreading, or squatting techniques) and bladder training are also known to alleviate IC/PBS symptoms. Furthermore, personal care and stress reduction strategies contribute to overall symptom improvement and quality of life (Hanley et al., 2009; Weiss, 2001).

Oral treatment

Oral pharmacotherapy is a second-line treatment that should be administered in combination with conservative treatment methods. If conservative treatment does not correct the symptoms alone, oral pharmacological treatment such as pentosan polysulfate sodium (PPS), amitriptyline, hydroxyzine, cimetidine and cyclosporine A is administered as a treatment (Table 1.).

- **Pentosan polysulfate sodium (PPS)**

Pentosan polysulfate sodium (PPS) is the only oral pharmacotherapy agent approved by the US Food and Drug Administration (FDA) for the treatment of IC/PBS. The disorder is thought to be associated with disruption of the GAG layer covering the bladder urothelium. PPS, a synthetic sulfated polysaccharide, acts by restoring this damaged GAG layer and thereby reducing urothelial permeability. It is administered orally at a dose of 300 mg/day for 8 months. It is no longer widely recommended due to side effects such as diarrhea, vomiting, rectal bleeding, and ophthalmic effects (Garzon et al., 2020).

- **Tricyclic antidepressants**

Amitriptyline is a tricyclic antidepressant commonly used in the management of IC/PBS. It acts by blocking the reuptake of serotonin and norepinephrine. Although not specifically approved for IC/PBS, it is widely prescribed for neuropathic pain. Its anticholinergic side effects include blurred vision, dry mouth, constipation, weight gain, and sedation. Other oral agents may be used in combination with amitriptyline to enhance therapeutic outcomes (Garzon et al., 2020).

- **Histamine receptor antagonists**

It has been shown that mediators released from mast cells during hypersensitivity reactions can cause urinary symptoms. Histamine receptor antagonists have been reported to reduce mast cell activation in patients with IC/PBS. Cimetidine, an H2 receptor antagonist, provides significant improvement in suprapubic pain and nocturia (Dasgupta et al., 2001; Thilagarajah et al., 2001). Hydroxyzine, an H1 antagonist with anticholinergic activity, has been shown to have no significant difference from placebo, but it is effective in combination with PPS (Fall et al., 2008).

- **Immunosuppressants**

Significant elevations in proinflammatory chemokines and cytokines have been demonstrated in the urine and bladder tissue of patients with IC/PBS (Crane et al., 2019). Cyclosporine A (CyA), a calcineurin inhibitor that suppresses T cell activation, has been reported to be effective in patients refractory to single-agent or oral combination therapies, resulting in reduced pain, increased maximum bladder capacity, and improved voiding volume. However, despite its promising long-term therapeutic benefits, CyA is associated with adverse effects such as hypertension, nephrotoxicity, hyperglycemia, dyslipidemia, and neurotoxicity, as well as an increased risk of infection (Crescenze et al., 2017; Sairanen et al., 2004; Sairanen et al., 2005; Wang & Zhang, 2016).

- **AQX-1125 (Rosiptor)**

AQX-1125, an activator of SH2-containing inositol-5'-phosphatase 1 (SHIP1), has recently been investigated as a novel oral therapeutic agent for the treatment of IC/PBS. In women with moderate-to-severe IC/PBS, a significant reduction in pain and urinary symptoms was reported following 6 weeks of oral AQX-1125 treatment (Nickel et al., 2016; Nickel et al., 2019).

Table 1. Alternative oral pharmacological agents for the management of IC/PBS

Agent	Proposed Mechanism of Action	Evidence/Remarks	Key References
Pentosan polysulfate sodium (PPS)	Replenishment of the glycosaminoglycan (GAG) layer; epithelial barrier protection; mild anti-inflammatory effects	Most extensively studied oral agent; modest efficacy; long-term use may be limited by pigmentary maculopathy risk.	Clemens et al., 2022; Jhang et al., 2025
Amitriptyline	Tricyclic antidepressant with analgesic and neuromodulatory properties; antimuscarinic effects	Demonstrated symptom improvement in clinical trials; sedation and anticholinergic side effects are limiting factors.	Cacciatore et al., 2024; Hanno et al., 2011
Hydroxyzine	H1 receptor blockade; mast-cell modulation and anti-inflammatory effects	May be particularly beneficial in patients with mast cell–related pathophysiology	Clemens et al., 2022; Hanno et al., 2011
Cimetidine	H2 receptor blockade; modulation of mast cell activation and histamine pathways	Limited evidence; small-scale studies show partial symptom improvement	Cacciatore et al., 2024
Cyclosporine A	Calcineurin inhibition; suppression of T-cell–mediated inflammation	Shown effective in refractory cases with Hunner lesions; requires close monitoring for nephrotoxicity and immunosuppression	Jhang et al., 2025

Intravesical therapy

Intravesical therapy is a third-line treatment option. It involves direct instillation of therapeutic agents into the bladder via a catheter. It is often combined with low-pressure, short-term hydrodistension. It provides easy and safe access to the bladder for prolonged drug exposure. The advantages of intravesical therapy include prolonged contact time between the drug and the urothelium, reduced systemic side effects, urothelial repair, and higher drug concentrations in the bladder wall compared to systemic administration. Other pathologies must be ruled out before these treatments can be administered, and they are recommended when less invasive treatments have failed. In general, maintenance therapy is generally required in patients who show improvement in symptoms (Garzon et al., 2020). The most commonly used intravesical agents are dimethyl sulfoxide (DMSO), lidocaine, heparin, pentosan polysulfate sodium, chondroitin sulfate, hyaluronic acid, and Bacillus Calmette-Guerin (BCG) (Table 2.).

- **Dimethyl sulfoxide (DMSO) and lidocaine**

DMSO is the only intravesical therapeutic agent approved by the FDA for the management of IC/PBS, and is commonly administered in combination with other agents. It is considered the most widely used intravesical intervention. Although its precise mechanism of action has not been fully elucidated, DMSO is thought to act by attenuating inflammation, relaxing bladder smooth muscle, and modulating of mast cell-mediated inflammatory activity. The standard instillation procedure consists of administering 50 mL of a 50% DMSO solution into the bladder via a catheter. Although no universally accepted treatment protocol exists, the regimen is commonly applied once weekly for a six-week period (Garzon et al., 2020; Hanno et al., 2011). Lidocaine is a local anesthetic with anti-inflammatory properties that provides symptomatic improvement both alone and in combination with other intravesical agents. Intravesical lidocaine is recommended by clinical guidelines for short-term relief of acute symptom exacerbations (Nickel et al., 2009).

- **Heparin and pentosan polysulfate sodium (PPS)**

The pathogenesis of IC/PBS is thought to be related to abnormalities in the bladder urothelium caused by disruption of the GAG layer. Heparin is a polysaccharide, one of the components of the GAG layer covering the urothelium. It is thought that intravesical instillation of exogenous GAG components, either as monotherapy or in combination with other drugs, replenishes this disrupted GAG layer. Heparin has an anti-inflammatory effect and is known to induce urothelial growth, smooth muscle, and fibroblast proliferation. Improvement in symptoms has been reported in 56-73% of patients after intravesical heparin therapy (3 months). Clinical studies indicate that heparin is more effective when used in combination with other agents rather than when used as monotherapy (Garzon et al., 2020; Giusto et al., 2018).

PPS is a heparin analog used as an intravesical drug to restore the GAG layer, in addition to its oral use. The combination of both oral and intravesical administration has been shown to provide greater improvement (Garzon et al., 2020).

- **Chondroitin sulfate and hyaluronic acid (HA)**

Both chondroitin sulfate and hyaluronic acid are components of the GAG layer covering the urothelium, and intravesical administration restores the damaged protective barrier. The combined use of these agents rather than as monotherapy is recommended (Cox et al., 2016; Garzon et al., 2020; Thakkinstian & Nickel, 2013).

Hyaluronic acid is a glycoprotein that is an important component of the GAG layer. It alleviates the inflammatory process by both inhibiting leukocyte aggregation and blocking ICAM-1 receptors by binding to lymphocytes and endothelial cells. It has also been reported to suppress mast cell degranulation in IC/PBS. Similarly, chondroitin sulfate has been identified as a key component of the GAG layer of the bladder. When used to replenish the GAG layer, it is thought to be more beneficial than HA (Ha & Xu, 2017).

Due to the multifactorial etiology of IC/PBS, combined intravesical therapy is preferred to enhance the therapeutic efficacy. iAluRil, containing 1.6% hyaluronic acid and 2% chondroitin sulfate, is commonly used in formulations for this purpose. This mixture is administered intravesically once weekly for 8 weeks. No significant adverse effects have been reported associated with iAluRil combination therapy (Ha & Xu, 2017).

- **Bacillus Calmette-Guerin (BCG)**

IC/PBS is thought to represent an autoimmune condition based on its histopathological features and the presence of autoantibodies ~~in~~ similar to those in other autoimmune diseases. IC/PBS patients have been shown to exhibit five times higher interleukin-6 production levels. The exact mechanism of BCG therapy remains unclear, and considering BCG's side effect profile and low therapeutic benefit, its use in IC/PBS treatment is limited (Ha & Xu, 2017).

Botulinum toxin A (BTX-A)

Botulinum toxin, produced by Clostridium botulinum, is recognized as the most potent neurotoxin. However, when administered in controlled doses, it can be effective in several clinical conditions. The American Urological Association (AUA) recommends this treatment for refractory overactive bladder. The FDA approved botulinum toxin for the treatment of neurogenic detrusor overactivity and refractory overactive bladder in 2011 (Spinu et al., 2020).

Botulinum toxin A (BTX-A) is a neurotoxic protein that can be administered intravesically into the detrusor smooth muscle. It is suggested that it inhibits the release of the neurotransmitter acetylcholine from cholinergic afferent nerve terminals in the suburothelial layer of the bladder, thereby providing antinociceptive and anti-inflammatory activity (Chen & Kuo, 2020; Chuang et al., 2004). Despite its therapeutic efficacy, it also has adverse effects such as urinary tract infections, viral conditions, and increased residual volume after urination (Spinu et al., 2020). However, intravesical BTX-A injection is still considered a safe and effective treatment option even after repeated treatments due to the limited duration of effect (9-10 months) (Lee & Kuo, 2015; Pinto et al., 2013; Shie et al., 2012).

Table 2. Experimental and investigational intravesical agents for IC/PBS

Agent	Proposed Mechanism of Action	Evidence/Remarks	Key References
Hyaluronic acid	GAG layer replenishment; enhancement of epithelial barrier and mucosal repair	Multiple studies and meta-analyses show symptom reduction; heterogeneous protocols.	EAU Guidelines, 2025; Plotti et al., 2024
Chondroitin sulfate	Restoration of the urothelial GAG barrier	Often combined with HA; partial symptomatic benefit in clinical studies	Plotti et al., 2024
Heparin	Anti-inflammatory and barrier-protective effects	Mixed results; occasionally used in combination protocols	Hanno et al., 2011
Lidocaine	Local anesthetic; blockade of sensory afferent signaling	Provides short-term relief; recommended for symptom flares in EAU guidance	EAU Guidelines, 2025
Botulinum toxin A	Inhibition of acetylcholine release; sensory and motor neuromodulation	Randomized trials show improvement in pain and bladder capacity; repeated injections may be required	Cacciatore et al., 2024; Jhang et al., 2025
Resiniferatoxin (RTX)	TRPV1 receptor desensitization and afferent nerve modulation	Results from randomized studies are inconsistent; it remains investigational	Cacciatore et al., 2024
Experimental anti-inflammatory formulations (e.g., NF-κB inhibitors)	Modulation of inflammatory signaling pathways; reduction of neurotrophin expression	Preclinical and early clinical evidence only; promising preliminary outcomes	Jhang et al., 2025

EMERGING/NOVEL THERAPIES

IC/PBS is a complex disease, and its exact etiology is not yet fully understood. More research is being conducted to discover the underlying full pathology, and new treatment methods are being developed. Several emerging therapies have shown promising results in small randomized trials (Colemeadow et al., 2020).

Improved intravesical drug delivery systems

New methods aimed at enhancing intravesical drug delivery, such as liposomes, the lidocaine-releasing intravesical system (LiRIS), and nanoparticles, appear promising in early trials (Colemeadow et al., 2020).

Liposomes and liposomal drug delivery are thought to be a promising new treatment for lower urinary tract dysfunction. Liposomes are drug carriers composed of phospholipids and sphingomyelins. They can adhere to the urothelium membrane surface and, after intravesical administration, support endocytosis by facilitating the entry of drugs, toxins, and oligonucleotides into the epithelium. When administered, they form a film layer that acts as a mechanical barrier in the bladder urothelium. They have been found to reduce inflammation and irritation in IC/PBS bladders and have been reported to renew the GAG layer by 50%. Although liposomes are ineffective when compared to a placebo, they have been considered as a carrier for botulinum toxin A in refractory IC/PBS patients as an alternative to injection (Garzon et al., 2020). Due to the large size of botulinum toxin A (150 kDa), it cannot access the afferent nerves immediately below without injection. The transport of the toxin from the urothelium to the deeper layers of the bladder is limited. Therefore, it has been combined with liposomes to enable the transport of Botulinum A to deeper layers (Chuang et al., 2009).

The goal is to transport Botulinum A from the urothelium via liposomes and to protect Botulinum A encapsulated within the liposomes from being broken down by proteases in urine without altering its efficacy (Chuang et al., 2009). Improvement was found to be 54% in the lipo-Botulinum A group and 32% in the placebo group, with no urinary retention or other side effects observed in either group (Chuang et al., 2014).

Tacrolimus is a potent lipophilic immunosuppressive drug. It exerts its effect by inhibiting IL-2-dependent T cell activation. However, systemic tacrolimus administration causes side effects such as nephrotoxicity and hypertension. The low solubility of tacrolimus in water also limits its intravesical distribution for treatment. Studies have shown that when liposomes are used for tacrolimus delivery, serum levels are low, while tacrolimus levels accumulated in the bladder are almost the same (Nirmal et al., 2013; Rajaganapathy et al., 2015).

Another slow-release drug delivery system, the lidocaine-releasing intravesical system (LiRIS), aims to provide continuous release of lidocaine over 2 weeks. A single-arm pilot study reported promising short-term efficacy in pain and urinary symptoms with a 64% success rate (Colemeadow et al., 2020).

Nanoparticles are widely used in the treatment of bladder diseases due to their controllable release kinetics and long-term drug retention advantages. They enable drugs to penetrate the bladder wall without damaging the urothelium structure (Sharif et al., 2019). Regulating mucoadhesion is essential to increase drug penetration. The combination of chitosan and haloysite nanotubes has been shown to improve mucoadhesion and control drug release (Barthelmes et al., 2011). Trimethoprim has also been incorporated into chitosan-thioglycolic acid nanoparticles to improve the therapeutic outcome of IC/PBS. The efficacy of trimethoprim-loaded chitosan-thioglycolic acid nanoparticles was found to be 14 times higher. Nanoparticle technology has yielded successful results for improved therapeutic effects in IC/PBS (Sharif et al., 2019).

Silodosin

Stress plays a very important role in IC/PBS. Patients who experienced traumatic events in their early lives exhibit a distinct symptomatic phenotype char-

acterized by intense pain and high urinary frequency (Charrua et al., 2015a; Chiu et al., 2017). Symptoms worsen during stressful periods in IC/PBS patients. Pain triggered or exacerbated by stress is thought to be caused by increased norepinephrine, especially in IC/PBS patients. Studies have shown that stress increases the excitability of bladder nociceptors through the activation of alpha1-adrenergic receptors. Silodosin is a high-affinity alpha1-adrenergic receptor antagonist. It has been reported that a group of patients resistant to oral, systemic, and intravesical treatments respond well to silodosin (Charrua et al., 2015b).

Anti-tumor necrosis factor-alpha (TNF-α) agents

Adalimumab is a biological agent known as an anti-tumor necrosis factor-alpha (TNF-α) agent or TNF-α blocking agent, which is a proinflammatory cytokine. Adalimumab is a recombinant monoclonal antibody that acts by neutralizing human TNF-α. Although a 53% success rate was recorded in a study with Adalimumab, a monoclonal antibody against the proinflammatory cytokine TNF-α, there was no significant difference compared to placebo due to the high placebo response in this study (Bosch, 2014).

Certolizumab pegol is a new anti-TNF-α agent used in the treatment of autoimmune diseases. Certolizumab pegol is thought to have potential advantages over other TNF-α antagonists in the treatment of IC/PBS. In a study with certolizumab pegol, there was a significant reduction in IC/PBS symptoms at week 18 (Di et al., 2021).

Anti-nerve growth factor (NGF) agents

Nerve growth factor (NGF) is one of the key factors contributing to the survival of sensory and sympathetic neurons during growth and is thought to be a peripheral mediator of various inflammatory painful conditions. It has been reported to be elevated in the urine and bladder tissue of IC/PBS patients. NGF increases bladder hyperactivity by sensitizing peripheral and central nerve endings (Hefti et al., 2006; Schnegelsberg et al., 2010). Recently, tanezumab, an anti-NGF agent, exerts its effect by blocking the interaction of NGF receptors with tropomyosin-related kinase A (high-affinity receptor) and p75 (low-affinity receptor). A study reported improvements in pain scores after 6 weeks of treatment (Abdiche et al., 2008; Brown et al., 2012; Evans et al., 2011).

Cannabinoids

Cannabinoids are known to have analgesic and anti-inflammatory properties and have been studied in various chronic pain conditions. In mouse models, activation of the cannabinoid 2 receptor has been shown to reduce the severity of chronic cystitis (Krenn et al., 2003).

Phosphodiesterase-5 inhibitors

Phosphodiesterase-5 (PDE5) inhibitors are thought to inhibit smooth muscle contraction and prevent mast cell degranulation by inhibiting potassium release. In a study of 48 women given low-dose PDE5 inhibitor sildenafil, improvements in urodynamic bladder capacity were observed after 3 months of treatment, and no serious side effects were seen (Chen et al., 2014).

CONCLUSION

IC/PBS is a multifactorial and a complex syndrome, together with pelvic pain, frequent urination, and urgency symptoms, the etiology of which is not yet fully understood, and for which there is no definitive treatment yet. After patients are correctly diagnosed, personalizing treatment with a multifaceted, individualized approach is key to managing the disease effectively. Conservative treatment, including patient education, behavioral modification, dietary advice, stress reduction and, physical therapy, is a fundamental initial management strategy for all patients. If conservative treatment is ineffective, oral treatments such as amitriptyline, pentosan polysulfate sodium, cimetidine and, hydroxyzine are initiated. Among oral treatments, amitriptyline may yield the best response. However, its side effects are not tolerated by the majority of patients. Although there is insufficient evidence for hydroxyzine and cimetidine, they may be included

in treatment due to their low incidence of side effects. The new SH2-containing inositol-5'-phosphatase 1 (SHIP1) activator AQX-1125 initially showed promising results, ~~but~~ trials concluded that it is a safe but ineffective therapeutic agent. Intravesical drug therapy is tried if less invasive treatments fail. Although DMSO shows a high recovery rate, symptoms return within 8 weeks in more than 35% of patients. The combined use of heparin and lidocaine has been reported to yield significantly effective results. Pentosan polysulfate sodium provides greater improvement when administered orally and intravesically at the same time, but it has many side effects. Studies support the combined intravesical administration of chondroitin and hyaluronic acid. Botulinum toxin A is tried if previous treatment steps fail and the patient is willing to risk catheterization, but viral infections observed after this therapy restrict its use. Oral cyclosporine is effective even in patients who have failed multiple oral treatments. However, it generally causes significant side effects, requiring intensive monitoring, and therefore cannot be widely used.

The use of liposomes and lidocaine-releasing intravesical system (LiRIS), newly developed drug delivery systems for IC/PBS, appears promising in early trials. Tacrolimus delivered via liposomes has been shown to have the same effect without systemic side effects. When the newly researched drug, alpha1-adrenoceptor antagonist silodosin, was administered, significant improvement was seen in 65% of patients in the experimental group. When sildenafil, a phosphodiesterase-5 inhibitor, was given to patients, improvements in bladder capacity were seen, and no serious side effects were observed. Adalimumab, one of the monoclonal antibodies, showed no significant difference compared to placebo. In studies with certolizumab pegol, superior benefit was demonstrated compared to placebo. In a study conducted for tanezumab, improvements in pain scores were recorded. The goal of most treatments used in clinics today is unfortunately, to control symptoms only; therefore, further experimental studies are needed to develop new effective drugs.

AUTHOR CONTRIBUTION STATEMENT

Literature research and writing (MD), Reviewing the text (NTDK).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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